Application No. 10/612,497
Reply to March 15, 2005 Office Action
Reply Dated April 21, 2005

Amendments to the Specification:

Please replace the title on page 1, line 1 with the following title:

Methods For Producing Human Monoclonal Antibodies To CTLA-4

Please replace the paragraph from page 1, lines 8-11, with the following amended paragraph:

The present application is a divisional application of U.S. Patent Application 09/472,087, filed December 23, 1999, now U.S. Patent 6,682,736, which claims priority to U.S. Provisional Patent Application 60/113,647, filed December 23, 1998, the disclosures of which are hereby incorporated in their entirety herein.

Please replace the paragraphs from page 11 line 1 to page 12, line 12, with the following amended paragraphs:

Figure 2 provides a sequence alignment between the predicted heavy chain amino acid sequences from the clones 4.1.1 <u>(SEQ ID NO: 74)</u>, 4.8.1 <u>(SEQ ID NO: 75)</u>, 4.14.3 <u>(SEQ ID NO: 78)</u>, 6.1.1 <u>(SEQ ID NO: 79)</u>, 3.1.1 <u>(SEQ ID NO: 73)</u>, 4.10.2 <u>(SEQ ID NO: 76)</u>, 4.13.1 <u>(SEQ ID NO: 77)</u>, 11.2.1 <u>(SEQ ID NO: 80)</u>, 11.6.1 <u>(SEQ ID NO: 81)</u>, 11.7.1 <u>(SEQ ID NO: 82)</u>, 12.3.1.1 <u>(SEQ ID NO: 83)</u>, and 12.9.1.1 <u>(SEQ ID NO: 84)</u> and the germline DP-50 (3-33) amino acid sequence <u>(SEQ ID NO: 72)</u>. Differences between the DP-50 germline sequence and that of the

sequence in the clones are indicated in bold. The Figure also shows the positions of the CDR1, CDR2, and CDR3 sequences of the antibodies as shaded.

Figure 3 provides a sequence alignment between the predicted heavy chain amino acid sequence of the clone 2.1.3 (SEQ ID NO: 86) and the germline DP-65 (4-31) amino acid sequence (SEQ ID NO: 85). Differences between the DP-65 germline sequence and that of the sequence in the clone are indicated in bold. The Figure also shows the positions of the CDR1, CDR2, and CDR3 sequences of the antibody as underlined.

Figure 4 provides a sequence alignment between the predicted kappa light chain amino acid sequence of the clones 4.1.1 (SEQ ID NO: 88), 4.8.1 (SEQ ID NO: 89), 4.14.3 (SEQ ID NO: 90), 6.1.1 (SEQ ID NO: 91), 4.10.2 (SEQ ID NO: 92), and 4.13.1 (SEQ ID NO: 93) and the germline A27 amino acid sequence (SEQ ID NO: 87). Differences between the A27 germline sequence and that of the sequence in the clone are indicated in bold. The Figure also shows the positions of the CDR1, CDR2, and CDR3 sequences of the antibody as underlined. Apparent deletions in the CDR1s of clones 4.8.1, 4.14.3, and 6.1.1 are indicated with "0s".

Figure 5 provides a sequence alignment between the predicted kappa light chain amino acid sequence of the clones 3.1.1 (SEQ ID NO: 95), 11.2.1 (SEQ ID NO: 96), 11.6.1 (SEQ ID NO: 97), and 11.7.1 (SEQ ID NO: 98) and the germline 012 amino acid sequence (SEQ ID NO: 94). Differences between the 012 germline sequence and that of the sequence in the clone are

indicated in bold. The Figure also shows the positions of the CDR1, CDR2, and CDR3 sequences of the antibody as underlined.

Figure 6 provides a sequence alignment between the predicted kappa light chain amino acid sequence of the clone 2.1.3 (SEQ ID NO: 112) and the germline A10/A26 amino acid sequence (SEQ ID NO: 99). Differences between the A10/A26 germline sequence and that of the sequence in the clone are indicated in bold. The Figure also shows the positions of the CDR1, CDR2, and CDR3 sequences of the antibody as underlined.

Figure 7 provides a sequence alignment between the predicted kappa light chain amino acid sequence of the clone 12.3.1 (SEQ ID NO: 114) and the germline A17 amino acid sequence (SEQ ID NO: 113). Differences between the A17 germline sequence and that of the sequence in the clone are indicated in bold. The Figure also shows the positions of the CDR1, CDR2, and CDR3 sequences of the antibody as underlined.

Figure 8 provides a sequence alignment between the predicted kappa light chain amino acid sequence of the clone 12.9.1 (SEQ ID NO: 116) and the germline A3/A19 amino acid sequence (SEQ ID NO: 115). Differences between the A3/A19 germline sequence and that of the sequence in the clone are indicated in bold. The Figure also shows the positions of the CDR1, CDR2, and CDR3 sequences of the antibody as underlined.

Please replace the paragraph from page 30, lines 9-31, with the following amended paragraph:

Peptide analogs are commonly used in the pharmaceutical industry as non-peptide ~~drus~~ drugs with properties analogous to those of the template peptide. These types of non-peptide compound are termed "peptide mimetics" or "peptidomimetics". Fauchere, *J. Adv. Drug Res.* 15:29 (1986); Veber and Freidinger *TINS* p.392 (1985); and Evans et al. *J. Med. Chem.* **30**:1229 (1987), which are incorporated herein by reference. Such compounds are often developed with the aid of computerized molecular modeling. Peptide mimetics that are structurally similar to therapeutically useful peptides may be used to produce an equivalent therapeutic or prophylactic effect. Generally, peptidomimetics are structurally similar to a paradigm polypeptide (i.e., a polypeptide that has a biochemical property or pharmacological activity), such as human antibody, but have one or more peptide linkages optionally replaced by a linkage selected from the group consisting of: --CH_2NH--, --CH_2S--, --CH_2-CH_2--, --CH=CH--(cis and trans), --$COCH_2$--, --CH(OH)CH_2--, and --CH_2SO--, by methods well known in the art. Systematic substitution of one or more amino acids of a consensus sequence with a D-amino acid of the same type (e.g., D-lysine in place of L-lysine) may be used to generate more stable peptides. In addition, constrained peptides comprising a consensus sequence or a substantially identical consensus sequence variation may be generated by methods known in the art (Rizo and Gierasch *Ann. Rev. Biochem.* **61**:387 (1992), incorporated herein by reference); for example, by adding internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

Please replace the paragraph from page 36, lines 6-29, with the following amended paragraph:

This general strategy was demonstrated in connection with our generation of the first ~~XenoMouse~~XENOMOUSE® mouse strains as published in 1994. *See* Green et al. *Nature Genetics* 7:13-21 (1994). The ~~XenoMouse~~XENOMOUSE® mouse strains were engineered with yeast artificial chromosomes (YACs) containing 245 kb and 190 kb-sized germline configuration fragments of the human heavy chain locus and kappa light chain locus, respectively, which contained core variable and constant region sequences. *Id.* The human Ig containing YACs proved to be compatible with the mouse system for both rearrangement and expression of antibodies and were capable of substituting for the inactivated mouse Ig genes. This was demonstrated by their ability to induce B-cell development, to produce an adult-like human repertoire of fully human antibodies, and to generate antigen-specific human Mabs. These results also suggested that introduction of larger portions of the human Ig loci containing greater numbers of V genes, additional regulatory elements, and human Ig constant regions might recapitulate substantially the full repertoire that is characteristic of the human humoral response to infection and immunization. The work of Green et al. was recently extended to the introduction of greater than approximately 80% of the human antibody repertoire through introduction of megabase sized, germline configuration YAC fragments of the human heavy chain loci and kappa light chain loci, respectively, to produce ~~XenoMouse~~XENOMOUSE® mice. *See* Mendez et al. *Nature Genetics* 15:146-156 (1997), Green and Jakobovits *J. Exp. Med.* 188:483-495 (1998), and

U.S. Patent Application Serial No. 08/759,620, filed December 3, 1996, the disclosures of which are hereby incorporated by reference.

Please replace the paragraph from page 47, lines 1-2, with the following amended paragraph:

Further, combinatorial libraries can be designed and ~~sythesized~~ synthesized and used in screening programs, such as high throughput screening efforts.

Please replace the paragraph from page 47, lines 6-25, with the following amended paragraph:

It will be appreciated that administration of therapeutic entities in accordance with the invention will be administered with suitable carriers, excipients, and other agents that are incorporated into formulations to provide improved transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences (15th ed, Mack Publishing Company, Easton, PA (1975)), particularly Chapter 87 by Blaug, Seymour, therein. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as ~~Lipofectin~~LIPOFECTIN^{TM} vesicles), DNA conjugates, anhydrous